ClinicalEvidence

Essential tremor

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ABSTRACT

INTRODUCTION: Essential tremor is one of the most common movement disorders in the world, with prevalence in the general population of 0.4% to 3.9%. METHODS AND OUTCOMES: We conducted a systematic overview, aiming to answer the following clinical question: What are the effects of drug treatments in people with essential tremor of the hand? We searched: Medline, Embase, The Cochrane Library, and other important databases up to January 2014 (BMJ Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview). RESULTS: At this update, searching of electronic databases retrieved 56 studies. After deduplication and removal of conference abstracts, 31 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 18 studies and the further review of 13 full publications. Of the 13 full articles evaluated, two RCTs were added at this update. We performed a GRADE evaluation for 11 PICO combinations. CONCLUSIONS: In this systematic overview, we categorised the efficacy for 13 interventions based on information about the effectiveness and safety of alprazolam, beta-blockers other than propranolol, botulinum A toxin-haemagglutinin complex, clonazepam, diazepam, gabapentin, levetiracetam, lorazepam, phenobarbital, primidone, propranolol, sodium oxybate, and topiramate.

QUESTIONS

INTERVENTIONS

DRUG TREATMENT

Key points

- Essential tremor refers to a persistent bilateral oscillation of both hands and forearms or an isolated tremor of the head, without abnormal posturing, and when there is no evidence that the tremor arises from another identifiable cause.

  Essential tremor is one of the most common movement disorders in the world, with a prevalence of 0.4% to 3.9% in the general population.

  Although most people with essential tremor are only mildly affected, it can be very disabling as the disease progresses and can cause physical and psychosocial impairment. Essential tremor commonly interferes with physical activities, including writing, using a computer, fixing small things, dressing, eating, and holding reading material.

- For this overview, we have examined the evidence from RCTs and systematic reviews of RCTs on the effects of selected drug treatments for essential tremor of the hand. There are other types of surgical interventions that may be used, such as deep brain stimulation or thalamotomy, but for this update we decided to focus on pharmacological therapies only because these are usually offered as initial treatment.

  Overall, we found few RCTs assessing the long-term effects of drug treatments.

  Many of the RCTs we found were small, short-term, and were crossover in design.

  Most of the RCTs were old, with few being published recently.

- Propranolol seems to effectively improve clinical scores, tremor amplitude, and self-evaluation of severity compared with placebo in people with hand tremor. However, the evidence comes from small RCTs, mostly of a crossover design, that only reported on results in the short term.

  Propranolol may have adverse effects, including hypotension and depression, that need to be considered before starting treatment.

  We didn't find sufficient evidence to judge the efficacy of other beta-blockers such as atenolol, metoprolol, nadolol, pindolol, and sotalol in treating essential tremor of the hand.

- Primidone may improve hand tremor in the short term for up to 10 weeks, but may be associated with depression and with cognitive and behavioural adverse effects.
- We found insufficient evidence on the effects of phenobarbital.
- We also found insufficient evidence on the effects of alprazolam and clonazepam, and no RCTs on the effects of diazepam and lorazepam.

  Benzodiazepines are associated with adverse effects such as dependency, sedation, and cognitive and behavioural effects.
- We don't know whether gabapentin is useful in treating essential tremor of the hand, as studies were small and the results were inconsistent.
- Botulinum A toxin-haemagglutinin complex and topiramate both appear to improve clinical rating scales for hand tremor in the short term, but are associated with frequent adverse effects.

  Botulinum A toxin-haemagglutinin complex is associated with hand weakness, which is dose-dependent and transient.

  Adverse effects of topiramate include appetite suppression, weight loss, and paraesthesia.
- We found insufficient evidence to draw reliable conclusions on the effects of levetiracetam and sodium oxybate.

Clinical context

GENERAL BACKGROUND

Essential tremor is a disabling neurological disorder. Although most people with essential tremor are only mildly affected, it can be very disabling as the disease progresses and can cause physical and psychosocial impairment. Essential tremor commonly interferes with physical activities, including writing, using a computer, fixing small things, dressing, eating, and holding reading material.

FOCUS OF THE REVIEW

A review of evidence for interventions for essential tremor is helpful for healthcare providers when considering the many possible medications available as well as other types of treatment, including deep brain stimulation. We have decided to focus this overview on some of the more commonly used pharmacological therapies for essential tremor because drug therapies are usually offered as initial therapy.

COMMENTS ON EVIDENCE

Overall, we found few RCTs assessing the long-term effects of drug treatments. Many of the trials we found were small, short term, and were crossover in design. In addition, most of the trials were old, with few published recently.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this overview was carried out from the date of the last search, December 2006, to January 2014. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the overview, please see the Methods section. Searching of electronic databases retrieved 56 studies. After deduplication and removal of conference abstracts, 31 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 18 studies and the further review of 13 full publications. Of the 13 full articles evaluated, two RCTs were added at this update.

ADDITIONAL INFORMATION

All medications have a trade-off between benefit and side effects. For example, propranolol can cause depression and hypotension, primidone can cause problems with initial titration and the side effects can be difficult to manage, and alprazolam has abuse potential. Adverse effects may be particularly difficult to manage in older patients. Propranolol and primidone are recommended in clinical guidelines as the first-line pharmacological therapy for essential tremor, but still a significant portion of patients might not respond. There are also multiple medications that have not been found beneficial for tremor. More effective pharmacological therapy is needed.

DEFINITION Tremor is a rhythmic, mechanical oscillation of at least one body region. The term 'essential tremor' is used when there is either a persistent bilateral tremor of hands and forearms or an isolated tremor of the head, without abnormal posturing, and when there is no evidence that the tremor arises from another identifiable cause. The diagnosis is not made if there are abnormal neurological signs, known causes of enhanced physiological tremor, a history or signs of psychogenic tremor, sudden change in severity, primary orthostatic tremor, isolated voice tremor, isolated position-specific or task-specific tremors, and isolated tongue, chin, or leg tremor. [1]

INCIDENCE/ PREVALENCE

Essential tremor is one of the most common movement disorders in the world, with a prevalence of 0.4% to 3.9% in the general population. [2]

AETIOLOGY/ RISK FACTORS

Essential tremor is sometimes inherited with an autosomal dominant pattern. About 40% of people with essential tremor have no family history of the condition. Alcohol ingestion provides symptomatic benefit in 50% to 70% of people. [3]

PROGNOSIS

Essential tremor is a persistent and progressive condition. It usually begins during early adulthood and the severity of the tremor slowly increases. Only a small proportion of people with essential tremor seek medical advice. [4] Although most people with essential tremor are only mildly affected, it can be very disabling as the disease progresses and can cause physical and psychosocial impairment. Most of the people who seek medical care are disabled to some extent, and most are socially handicapped by the tremor. [3] One quarter of people receiving medical care for the tremor change jobs or retire because of essential tremor-induced disability. [5] [6] Essential tremor frequently causes embarrassment and limits patients socially.

AIMS OF INTERVENTION

To reduce tremor; to minimise disability and social embarrassment; to improve quality of life, with minimal adverse effects from treatment.

OUTCOMES

Tremor severity measured by clinical rating scales or patient self-evaluation. Clinical rating scales are often composite scores that grade tremor amplitude in each body segment in specific postures or tasks. Few scales have been formally validated. In more recent trials, the Fahn-Tolosa-Marin clinical evaluation scale, [7] which addresses the impairment and the disability domains of tremor, has become the preferred scale. The WHIGET and TETRAS scales have also been developed. Accelerometer recordings are reported in many trials, but they are proxy outcomes. **Adverse effects**.

METHODS

Search strategy *BMJ Clinical Evidence* search and appraisal date January 2014. Databases used to identify studies for this systematic overview include: Medline 1966 to January 2014, Embase 1980 to January 2014, The Cochrane Database of Systematic Reviews 2013, issue 12 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. **Inclusion criteria** Study design criteria for inclusion in this systematic overview were systematic reviews and RCTs published in English, and at least single-blinded. There was no minimum sample size and no maximum loss to follow-up. There was a minimum length of follow-up of 1 week. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. We excluded single-dose studies and RCTs lasting under 1 week. We included small RCTs because of the paucity of evidence in this population. Most of the RCTs we identified used a crossover design. While this design is useful in situations such as tremor (believed to be relatively constant despite the existence of fluctuations), because it allows an intrasubject comparison, thereby increasing the power of the analysis, it can be confounded by factors such as carry-over of the effect seen before the crossover to the post-crossover period. Also, because the effect is dependent on the moment of administration, this means that effects of an intervention may differ in the period before and after crossover. Since most of the studies do not assess results before crossover and do not explicitly address these confounders or the impact of withdrawals from the trial, it is very difficult to interpret the data provided completely. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant, and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed *a priori* with our expert contributors. In consultation with the expert contributors, studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the overview. In addition, information that did not meet our pre-defined criteria for inclusion in the benefits and harms section may have been reported in the 'Further information on studies' or 'Comment' section. **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributors may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robust-

ness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Structural changes this update** At this update, we have removed the following interventions from this overview: calcium channel blockers, carbonic anhydrase inhibitors, clonidine, flunarizine, isoniazid, mirtazapine; and we have added the following options: sodium oxybate and levetiracetam. We previously included benzodiazepines as an option, but at this update we have replaced this with the following more specific options: alprazolam, clonazepam, diazepam, and lorazepam. **Data and quality** To aid readability of the numerical data in our overviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue that may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 40). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of drug treatments in people with essential tremor of the hand?

OPTION ALPRAZOLAM New

- For GRADE evaluation of interventions for Essential tremor, see table, p 40 .
- We were unable to draw reliable conclusions on the effects of alprazolam, as we only found two small RCTs that met our inclusion criteria. There was no direct comparison between intervention groups for clinical and self-rating scores in either study.
- The 2011 American Academy of Neurology guideline on essential tremor recommends that alprazolam is "probably effective" in reducing limb tremor, but that it should be used with caution because of its abuse potential.
- In general, benzodiazepines are associated with adverse effects such as dependency and sedation. Cognitive and behavioural effects are common in older adult patients.

Benefits and harms

Alprazolam versus placebo:

We found two RCTs. [8] [9]

Tremor severity

Alprazolam compared with placebo We don't know whether alprazolam is more effective than placebo at improving tremor severity in people with essential tremor of the hand (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical scores					
[9] RCT	24 people	**Clinical scores , 2 weeks** with alprazolam with placebo Absolute results not reported No significant change from baseline reported with alprazolam	No direct comparison between groups, but assessed changes from baseline within each group		
[9] RCT	24 people	**Observer-rated global impression , 2 weeks** with alprazolam with placebo Absolute results not reported	No direct comparison between groups, but assessed changes from baseline within each group		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Alprazolam improved observer-rated global impression to a greater extent from baseline compared with placebo			
Self-rating					
[9] RCT	24 people	**Self-evaluation of tremor , 2 weeks** with alprazolam with placebo Absolute results not reported No significant change from baseline reported with alprazolam	No direct comparison between groups, but assessed changes from baseline within each group		
Performance tests					
[8] RCT **Crossover design** **4-armed trial**	22 people	**Observer-rated score (0 = normal, 11 = unable to keep pencil on paper, needs help to feed, and no social activity) , 4 weeks** 6.0 with alprazolam 7.8 with placebo Results before crossover The remaining arms evaluated acetazolamide and primidone	P value not reported		
[9] RCT	24 people	**Functional tests , 2 weeks** with alprazolam with placebo Absolute results not reported No significant change from baseline reported with alprazolam	No direct comparison between groups, but assessed changes from baseline within each group		

Adverse effects

No data from the following reference on this outcome. [8] [9]

Comment: We found no RCTs addressing long-term outcomes. Adverse effects with benzodiazepines, including dependency, sedation, and cognitive and behavioural effects, have been well described for other conditions.

Clinical guide
The American Academy of Neurology 2011 guideline update on the treatment of essential tremor reported that alprazolam is "probably effective" in reducing limb tremor, based on the two RCTs we have included in this option. [8] [9] [10] However, the guideline also includes a statement that it should be used with caution because of its abuse potential. Alprazolam should not be used in the long-term treatment for essential tremor due to its short-acting nature and the tendency of dependence. However, alprazolam might be used on an 'as needed' basis (e.g., 30 minutes to 1 hour before a stressful situation that might worsen the tremor).

OPTION BETA-BLOCKERS OTHER THAN PROPRANOLOL

- For GRADE evaluation of interventions for Essential tremor, see table, p 40 .
- We found insufficient evidence to judge the efficacy of beta-blockers other than propranolol (such as atenolol, metoprolol, nadolol, pindolol, and sotalol) in treating essential tremor (ET) of the hand, compared with placebo or with propranolol.

Benefits and harms

Beta-blockers other than propranolol versus placebo:

We found six small, brief crossover RCTs comparing different beta-blockers (atenolol, metoprolol, nadolol, pindolol, and sotalol) with placebo. [11] [12] [13] [14] [15] [16]

Tremor severity

Beta-blockers other than propranolol compared with placebo We don't know whether beta-blockers other than propranolol (trials included atenolol, metoprolol, nadolol, pindolol, and sotalol) are more effective than placebo at improving tremor scores in people with essential tremor of the hand, as we found insufficient evidence from small, brief RCTs (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical scores					
[11] RCT **Crossover design**	16 people with ET (16 completed), clinical diagnosis 15 of the participants in this RCT had previously participated in RCT [17]	**Clinical score** with metoprolol 150 and 300 mg/day with placebo Absolute results reported graphically Propranolol and metoprolol were each given for two consecutive treatment periods (each lasting for 2 weeks) during which two dosage regimens were used: 120 and 240 mg daily for propranolol and 150 and 300 mg daily for metoprolol Results before crossover	P value reported as not significant	⟷	Not significant
[12] RCT **Crossover design** **4-armed trial**	9 people with ET (9 completed), clinical diagnosis	**Mean clinical score (0–25)** 6.8 with sotalol 8.1 with atenolol 10.7 with placebo Results assessed after crossover; no washout period between drugs The remaining arm evaluated propranolol	P <0.01 (sotalol *v* placebo) P <0.002 (atenolol *v* placebo)	○○○	other beta-blockers (sotalol or atenolol)
[15] RCT **Crossover design**	10 people with ET (10 completed), stratified for response to propranolol: 6 responders, 4 non-responders, clinical diagnosis	**Clinical scores** with nadolol with placebo Each treatment period was 4 weeks, with 1 week washout between treatments, total duration of 10 weeks	Nadolol not directly compared with placebo; analysis of change in each group from baseline Clinical scores improved in those that were responders to propranolol		
[16] RCT **Crossover design** **4-armed trial**	24 people with ET (24 completed), clinical diagnosis	**Clinical score: % improvement in objective clinical scores** 4.5% with metoprolol 50 mg (17 people) or 100 mg (7 people) 0% with placebo (ascorbic acid 50 mg)	P value reported as not significant	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Clinical score: Scores (0–5) for 3 tasks (handwriting, spiral, and sinusoidal drawings) were calculated both by an assessor and by an observer and added to get a final clinical score (maximum 30 points) Each treatment period was 4 weeks, total duration of 4 weeks The remaining arms evaluated sotalol (50 mg/day) and atenolol (50 mg/day)			
[16] RCT **Crossover design** **4-armed trial**	24 people with ET (24 completed), clinical diagnosis	**Clinical score: % improvement in objective clinical scores** 20% with sotalol 50 mg/day 0% with placebo (ascorbic acid 50 mg) Clinical score: Scores (0–5) for 3 tasks (handwriting, spiral, and sinusoidal drawings) were calculated both by an assessor and by an observer and added to get a final clinical score (maximum 30 points) Each treatment period was 4 weeks, total duration of 4 weeks The remaining arms evaluated metoprolol (50 mg or 100 mg) and atenolol (50 mg/day)	P <0.01 (sotalol *v* placebo)	○○○	sotalol
[16] RCT **Crossover design** **4-armed trial**	24 people with ET (24 completed), clinical diagnosis	**Clinical score: % improvement in objective clinical scores** 16% with atenolol 50 mg/day 0% with placebo (ascorbic acid 50 mg) Clinical score: Scores (0–5) for 3 tasks (handwriting, spiral, and sinusoidal drawings) were calculated both by an assessor and by an observer and added to get a final clinical score (maximum 30 points) Each treatment period was 4 weeks, total duration of 4 weeks The remaining arms evaluated metoprolol (50 mg or 100 mg) and sotalol (50 mg/day)	P <0.01 (atenolol *v* placebo)	○○○	atenolol
Accelerometry					
[11] RCT **Crossover design**	16 people with ET (16 completed), clinical diagnosis 15 of the participants in this RCT had previously participated in RCT [17]	**Accelerometry (amplitude)** with metoprolol 150 and 300 mg/day with placebo Absolute results reported graphically Propranolol and metoprolol were each given for two consecutive treatment periods (each lasting for 2 weeks) during which two dosage regimens were used: 120 and 240 mg daily for propranolol and 150 and 300 mg daily for metoprolol	P value reported as not significant	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Results before crossover			
[13] RCT **Crossover design** **3-armed trial**	24 people with ET (24 completed), clinical diagnosis	**Accelerometry (frequency)** 9.7 with pindolol for 5–7 days 9.9 with placebo for 5–7 days 1 week washout between treatments, total duration of 6 weeks Results after crossover The remaining arm evaluated propranolol (for 5–7 days)	Reported as not significant P value not reported	⟷	Not significant
[13] RCT **Crossover design** **3-armed trial**	24 people with ET (24 completed), clinical diagnosis	**Accelerometry (maximum amplitude)** 160 with pindolol 105 with placebo for 5–7 days 1 week washout between treatments, total duration of 6 weeks Results after crossover The remaining arm evaluated propranolol (for 5–7 days)	P <0.05 (pindolol *v* placebo)	○○○	placebo
[14] RCT **Crossover design** **3-armed trial**	24 people with ET (24 completed), clinical diagnosis	**Accelerometry (reduction in tremor intensity; % decrease from baseline)** 37.3 with atenolol 4.9 with placebo Results after crossover; 1 week crossover between drugs The remaining arm evaluated propranolol	P <0.001 (atenolol *v* placebo)	○○○	atenolol
[15] RCT **Crossover design**	10 people with ET (10 completed), stratified for response to propranolol: 6 responders, 4 non-responders, clinical diagnosis	**Accelerometry (tremor frequency)** with nadolol with placebo Each treatment period was 4 weeks, with 1 week washout between treatments, total duration of 10 weeks	Nadolol not directly compared with placebo; analysis of change in each group from baseline No significant change from baseline between nadolol at both doses and placebo in four people who had previously not responded to propranolol Significant improvement from baseline in 6 people who were responders to propranolol		
Self-rating					
[11] RCT **Crossover design**	16 people with ET (16 completed), clinical diagnosis 15 of the participants in this RCT had previously participated in RCT [17]	**Self-rating score (0–5)** with metoprolol 150 and 300 mg/day with placebo Absolute results reported graphically Propranolol and metoprolol were each given for two consecutive treatment periods (each lasting for 2 weeks) during which two dosage regimens were used: 120 and 240 mg daily for propranolol and 150 and 300 mg daily for metoprolol Results before crossover	P (metoprolol 150 or 300 mg/day *v* placebo) reported as not significant	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[12] RCT **Crossover design** **4-armed trial**	9 people with ET (9 completed), clinical diagnosis	**Mean subjective tremor score (0–10)** 4.2 with sotalol 6.2 with placebo Results assessed after crossover; no washout period between drugs The remaining arms evaluated propranolol and atenolol	P <0.05 (sotalol *v* placebo)	○○○	sotalol
[12] RCT **Crossover design** **4-armed trial**	9 people with ET (9 completed), clinical diagnosis	**Mean subjective tremor score (0–10)** 5.9 with atenolol 6.2 with placebo Results assessed after crossover; no washout period between drugs The remaining arms evaluated propranolol and sotalol	P = 0.1 (atenolol v placebo)	⟷	Not significant
[16] RCT **Crossover design** **4-armed trial**	24 people with ET (24 completed), clinical diagnosis	**Self-rating** with metoprolol 50 mg (17 people) or 100 mg (7 people) with sotalol 50 mg/day with atenolol 50 mg/day with placebo (ascorbic acid 50 mg) Absolute results reported graphically Self-assessment using VAS 100 mm scale	P <0.01 (sotalol *v* placebo) P <0.05 (atenolol or metoprolol *v* placebo)	○○○	other beta-blockers (sotalol, atenolol, metoprolol)
Performance tests					
[11] RCT **Crossover design**	16 people with ET (16 completed), clinical diagnosis 15 of the participants in this RCT had previously participated in RCT [17]	**Performance tests** with metoprolol 150 and 300 mg/day with placebo Absolute results reported graphically Propranolol and metoprolol were each given for two consecutive treatment periods (each lasting for 2 weeks) during which two dosage regimens were used: 120 and 240 mg daily for propranolol and 150 and 300 mg daily for metoprolol Results before crossover	P value (metoprolol 150 or 300 mg/day *v* placebo) reported as not significant	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[11] RCT **Crossover design**	16 people with ET (16 completed), clinical diagnosis	**Adverse effects** with metoprolol 150 and 300 mg/day with placebo			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	15 of the participants in this RCT had previously participated in RCT [17]	Propranolol and metoprolol were each given for two consecutive treatment periods (each lasting for 2 weeks) during which two dosage regimens were used: 120 and 240 mg daily for propranolol and 150 and 300 mg daily for metoprolol Similar proportions of people taking metoprolol or placebo had adverse effects, including breathlessness, palpitations, dizziness, tiredness, headache, and nausea			
[14] RCT **Crossover design** **3-armed trial**	24 people with ET (24 completed), clinical diagnosis	**Adverse effects** with atenolol with placebo Similar proportions of people taking atenolol or placebo had adverse effects, including breathlessness, palpitations, dizziness, tiredness, headache, and nausea The remaining arm evaluated propranolol			
[12] RCT **Crossover design** **4-armed trial**	9 people with ET (9 completed), clinical diagnosis	**Adverse effects** with sotalol with atenolol with placebo The RCT suggested that no one taking sotalol or atenolol had adverse effects The remaining arm evaluated propranolol			
[16] RCT **Crossover design** **4-armed trial**	24 people with ET (24 completed), clinical diagnosis	**Adverse effects** with metoprolol with sotalol with atenolol with placebo The RCT suggested that no one taking metoprolol, sotalol, or atenolol had adverse effects			
[15] RCT **Crossover design**	10 people with ET (10 completed), stratified for response to propranolol: 6 responders, 4 non-responders, clinical diagnosis	**Adverse effects** with nadolol with placebo The RCT suggested that no one taking nadolol had adverse effects			

No data from the following reference on this outcome. [13]

Beta-blockers other than propranolol versus propranolol:

We found no systematic review but found four small (16–24 people) [11] [12] [14] [18] and one large (175 people) [19] crossover RCT.

Tremor severity

Beta-blockers other than propranolol compared with propranolol We don't know how beta-blockers other than propranolol (trials included atenolol, metoprolol, sotalol, arotinolol) and propranolol compare at improving tremor in people with essential tremor of the hand. We found insufficient evidence to draw reliable conclusions (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical scores					
[11] RCT **Crossover design**	16 people with ET (16 completed), clinical diagnosis 15 of the participants in this RCT had previously participated in RCT [17]	**Clinical score** with metoprolol 150 and 300 mg/day with propranolol 120 and 240 mg/day Absolute results reported graphically Propranolol and metoprolol were each given for two consecutive treatment periods (each lasting for 2 weeks) during which two dosage regimens were used: 120 and 240 mg daily for propranolol and 150 and 300 mg daily for metoprolol The RCT included placebo as a comparator Results before crossover	P <0.05 (propranolol 120 mg *v* metoprolol 150 mg)	○○○	propranolol
[12] RCT **Crossover design** **4-armed trial**	9 people with ET (9 completed), clinical diagnosis	**Mean clinical score (0–25)** 6.8 with sotalol 6.6 with propranolol Results assessed after crossover; no washout period between drugs The remaining arms evaluated placebo and atenolol	P >0.1 (propranolol *v* sotalol)	⟷	Not significant
[12] RCT **Crossover design** **4-armed trial**	9 people with ET (9 completed), clinical diagnosis	**Mean clinical score (0–25)** 8.1 with atenolol 6.6 with propranolol Results assessed after crossover; no washout period between drugs The remaining arms evaluated placebo and sotalol	P <0.05 (propranolol *v* atenolol)	○○○	propranolol
[18] RCT **Crossover design**	23 people with essential tremor (20 completed), clinical diagnosis	**Proportion of people with clinical scores significantly improved from baseline** 13/23 (56%) with metoprolol 50, 150, or 250 mg/day 10/20 (50%) with propranolol 120 and 240 mg/day Each treatment period was 6 weeks, escalating doses every 2 weeks, with 1 week washout between treatments, total duration of 14 weeks	No direct comparison between propranolol and metoprolol		
Accelerometry					
[14] RCT	24 people with ET (24 completed), clinical diagnosis	**Accelerometry (tremor intensity; % decrease from baseline)** 42.9 with propranolol	Reported as not significant P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Crossover design **3-armed trial**		37.3 with atenolol Results after crossover; 1 week crossover between drugs The remaining arm evaluated placebo			
[18] RCT **Crossover design**	23 people with essential tremor (20 completed), clinical diagnosis	**Accelerometry (tremor amplitude)** with metoprolol 50, 150, or 250 mg/day with propranolol 120 and 240 mg/day Each treatment period was 6 weeks, escalating doses every 2 weeks, with 1 week washout between treatments, total duration of 14 weeks	No direct comparison between propranolol and metoprolol No significant improvement from baseline for propranolol or metoprolol; reported as not significant, no further data reported For the subgroup of the clinical responders there was a difference for both treatments; P <0.05		
Self-rating					
[12] RCT **Crossover design** **4-armed trial**	9 people with ET (9 completed), clinical diagnosis	**Mean subjective tremor score (0–10)** 4.2 with sotalol 4.4 with propranolol Results assessed after crossover; no washout period between drugs The remaining arms evaluated placebo and atenolol	P = 0.1 (propranolol *v* sotalol)	⟷	Not significant
[12] RCT **Crossover design** **4-armed trial**	9 people with ET (9 completed), clinical diagnosis	**Mean subjective tremor score (0–10)** 5.9 with atenolol 4.4 with propranolol Results assessed after crossover; no washout period between drugs The remaining arms evaluated placebo and sotalol	P <0.05 (propranolol *v* atenolol)	○○○	propranolol
[14] RCT **Crossover design** **3-armed trial**	24 people with ET (24 completed), clinical diagnosis	**Proportion of people preferring each treatment** 12/24 (50%) with propranolol 1/24 (4%) with atenolol Results after crossover; 1 week crossover between drugs The remaining arm evaluated placebo	P value not reported		
[18] RCT **Crossover design**	23 people with essential tremor (20 completed), clinical diagnosis	**Self-rating** with metoprolol 50, 150, or 250 mg/day with propranolol 120 and 240 mg/day Each treatment period was 6 weeks, escalating doses every 2 weeks, with 1 week washout between treatments, total duration of 14 weeks 11 people taking propranolol stated that they had improved, 8 found no change, and 1 worsened	No direct comparison between propranolol and metoprolol		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		14 people taking metoprolol improved and 9 found no change			
[19] RCT **Crossover design**	175 people with ET (145 completed), clinical diagnosis	**Self-reported disability scale score, dose-based comparison (Scale 0 to 100; where 0 to 24 = no change, 25 to 49 = mild improvement, 50 to 74 = moderate improvement, 75 to 100 = marked improvement) , 8–14 weeks** 9.78 with arotinolol 10 mg daily 10.12 with propranolol 40 mg daily 9.18 with arotinolol 20 mg daily 9.82 with propranolol 80 mg daily 8.90 with arotinolol 30 mg daily 9.38 with propranolol 160 mg daily Each treatment period was 6 weeks, escalating doses every 2 weeks, with a 2-week washout between treatments before crossover to the other drug, 2-week pre-randomisation washout, total duration of 16 weeks Analysis by intention to treat and adjusted to allow for crossover effects	Reported as not significant P values not reported	⟷	Not significant
Performance tests					
[11] RCT **Crossover design**	16 people with ET (16 completed), clinical diagnosis 15 of the participants in this RCT had previously participated in RCT [17]	**Performance tests** with metoprolol 150 and 300 mg/day with propranolol 120 and 240 mg/day Absolute results reported graphically Propranolol and metoprolol were each given for two consecutive treatment periods (each lasting for 2 weeks) during which two dosage regimens were used: 120 and 240 mg daily for propranolol and 150 and 300 mg daily for metoprolol The RCT included placebo as a comparator Results before crossover	P <0.05 (propranolol 120 mg *v* metoprolol 150 mg) P <0.05 (propranolol 240 mg *v* metoprolol 300 mg)	○○○	propranolol
[19] RCT **Crossover design**	175 people with ET (145 completed), clinical diagnosis	**Motor task performance score , 8 to 14 weeks** 8.63 with arotinolol 10 mg daily 8.35 with propranolol 40 mg daily 7.93 with arotinolol 20 mg daily 8.09 with propranolol 80 mg daily 7.52 with arotinolol 30 mg daily 7.65 with propranolol 160 mg daily Each treatment period was 6 weeks, escalating doses every 2 weeks, with a 2-week washout	Reported as not significant P values not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		between treatments before crossover to the other drug, 2-week pre-randomisation washout, total duration of 16 weeks Analysis by intention to treat and adjusted to allow for crossover effects			

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[11] RCT **Crossover design**	16 people with ET (16 completed), clinical diagnosis 15 of the participants in this RCT had previously participated in RCT [17]	**Adverse effects** with metoprolol 150 and 300 mg/day with propranolol 120 and 240 mg/day Propranolol and metoprolol were each given for two consecutive treatment periods (each lasting for 2 weeks) during which two dosage regimens were used: 120 and 240 mg daily for propranolol and 150 and 300 mg daily for metoprolol The RCT included placebo as a comparator Similar proportions of people taking metoprolol or propranolol had adverse effects, including tiredness, headache, and breathlessness			
[14] RCT **Crossover design** **3-armed trial**	24 people with ET (24 completed), clinical diagnosis	**Adverse effects** 42.9 with propranolol 37.3 with atenolol The third RCT found that similar proportions of people taking atenolol or propranolol had adverse effects, including tiredness, dizziness, and nausea The remaining arm evaluated placebo			
[18] RCT **Crossover design**	23 people with essential tremor (20 completed), clinical diagnosis	**Adverse effects** with metoprolol 50, 150, or 250 mg/day with propranolol 120 and 240 mg/day 3/20 (15%) people discontinued treatment with propranolol owing to breathlessness Both drugs were associated with headache, and propranolol was associated with dizziness, rash, and impotence			
[19] RCT	175 people with ET (145 completed), clinical diagnosis	**Proportion of people who had adverse effects during treatment**	P = 0.52	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Crossover design		10/175 (6%) with arotinolol 13/175 (7%) with propranolol 1 person taking propranolol was withdrawn from treatment because of severe bradycardia The most frequently reported adverse effects (occurring in >1% of people) were gastrointestinal discomfort (dyspepsia, diarrhoea, and gastric upset), bradycardia, headache, dizziness, sleep disturbance, and skin rash			

No data from the following reference on this outcome. [13]

Comment: People with congestive heart failure, second-degree heart block, asthma, severe allergy, and insulin-dependent diabetes were generally excluded from the RCTs. We found no RCTs addressing long-term outcomes.

Clinical guide
There is no sufficient evidence that beta-blockers other than propranolol are superior to or even equally effective as propranolol. So far, propranolol remains the beta-blocker with the most evidence to treat essential tremor and is recommended in clinical guidelines as a preferred beta-blocker for clinicians to treat essential tremor. [10]

OPTION BOTULINUM A TOXIN-HAEMAGGLUTININ COMPLEX

- For GRADE evaluation of interventions for Essential tremor, see table, p 40 .
- Botulinum A toxin-haemagglutinin complex appears to improve clinical rating scales for tremor in the short term (up to 12 weeks) in people with essential tremor of the hand, but is associated with frequent adverse effects.
- Hand weakness, which is dose-dependent and transient, is a frequent adverse effect.
- We found no direct information about long-term outcomes from botulinum A toxin-haemagglutinin complex in people with essential tremor of the hand.

Benefits and harms

Botulinum A toxin-haemagglutinin complex versus placebo:

We found no systematic reviews. We found two parallel RCTs. [20] [21]

Tremor severity

Botulinum A toxin-haemagglutinin complex compared with placebo Botulinum A toxin-haemagglutinin complex may be more effective than placebo at improving clinical scores and self-rating scores at up to 12 weeks in people with essential tremor of the hand, but we don't know about accelerometry scores, motor tests, or functional scores (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical scores					
[20] RCT	25 people with essential hand tremor unresponsive to "optimal medical therapy"	**Clinical scores** with botulinum A toxin–haemagglutinin complex with placebo	P <0.01	○○○	botulinum toxin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Botulinum toxin 50 U was injected in forearm muscles, and was repeated, if necessary, after 1 month (100 U).			
[21] RCT **3-armed trial**	133 people with essential tremor of the hand by the Tremor Investigation Group criteria	**Postural tremor on clinical rating scales , 12 weeks** with single injections of low-dose botulinum A toxin-haemagglutinin complex (50 U) with high-dose botulinum A toxin-haemagglutinin complex (100 U) with placebo Injected into the wrist flexors and extensors	P = 0.004 (low-dose botulinum toxin *v* placebo) P = 0.0003 (high-dose botulinum toxin *v* placebo)	○○○	botulinum toxin
Accelerometry					
[20] RCT	25 people with essential hand tremor unresponsive to "optimal medical therapy"	**Accelerometer recordings** with botulinum A toxin-haemagglutinin complex with placebo Botulinum toxin 50 U was injected in forearm muscles, and was repeated, if necessary, after 1 month (100 U).	Reported as not significant P value not reported	⟷	Not significant
Self-rating/undefined improvement					
[20] RCT	25 people with essential hand tremor unresponsive to "optimal medical therapy"	**Proportion of people who responded to first injection** 12/13 (92%) with botulinum A toxin-haemagglutinin complex 1/12 (8%) with placebo Botulinum toxin 50 U was injected in forearm muscles, and was repeated, if necessary, after 1 month (100 U).	P <0.001	○○○	botulinum toxin
[20] RCT	25 people with essential hand tremor unresponsive to "optimal medical therapy"	**Mild to moderate improvement , 4 weeks** 9/12 (75%) with botulinum A toxin-haemagglutinin complex 3/11 (27%) with placebo Botulinum toxin 50 U was injected in forearm muscles, and was repeated, if necessary, after 1 month (100 U).	P <0.04	○○○	botulinum toxin
Perfomance tests					
[20] RCT	25 people with essential hand tremor unresponsive to "optimal medical therapy"	**Functional tests (write a sentence, Archimedes' spirals, a straight line, a sine wave between lines, pour water into a cup)** with botulinum A toxin-haemagglutinin complex with placebo Botulinum toxin 50 U was injected in forearm muscles, and was repeated, if necessary, after 1 month (100 U).	Reported as not significant P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[21] RCT **3-armed trial**	133 people with essential tremor of the hand by the Tremor Investigation Group criteria	**Kinetic tremor, motor task performance, or functional disability , 16 weeks** with single injections of low-dose botulinum A toxin-haemagglutinin complex (50 U) with high-dose botulinum A toxin-haemagglutinin complex (100 U) with placebo Injected into the wrist flexors and extensors		⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [20] [21]

Further information on studies

[20] The RCT stated that participants were unresponsive to "optimal medical therapy", but did not state what this involved.

Comment: We found no RCTs addressing long-term outcomes. The main adverse effect of botulinum A toxin-haemagglutinin complex is dose-dependent transient hand weakness. The effectiveness of botulinum A toxin-haemagglutinin complex could be highly dependent on the site of injections and the dose used.

Clinical guide

Botulinum A toxin-haemagglutinin complex may be used in the patients with essential tremor of the hand who have large-amplitude and disabling tremor that is refractory to first-line therapy, such as propranolol and primidone. [22] However, in the two RCTs we found, the decreased tremor severity did not seem to be translated into functional improvement measured by performance testing. [20] [21] Therefore, botulinum A toxin-haemagglutinin complex might be more helpful for improving performance of simple tasks rather than complex tasks that require a high level of hand dexterity. Unlike other pharmacological therapy for essential tremor, botulinum A toxin-haemagglutinin complex acts mostly on the peripheral nervous system and does not have side effects affecting emotional state or cognition.

OPTION CLONAZEPAM New

- For GRADE evaluation of interventions for Essential tremor, see table, p 40 .
- We were unable to draw reliable conclusions on the effects of clonazepam. We only found one small RCT that met our inclusion criteria, which found no significant difference in tremor severity between clonazepam and placebo. The trial was probably underpowered to detect a clinically important difference in outcomes.
- In general, benzodiazepines are associated with adverse effects such as dependency, sedation, and cognitive and behavioural effects, although clonazepam is a longer-acting benzodiazepine and may have fewer side effects than shorter-acting agents.

Benefits and harms

Clonazepam versus placebo:

We found one RCT. [23]

Tremor severity

Clonazepam compared with placebo We don't know whether clonazepam is more effective than placebo at improving tremor severity in people with essential tremor of the hand (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Tremor outcomes					
[23] RCT **Crossover design**	15 people 9 people withdrew during an open run-in period with clonazepam, so only 6 entered the double-blind phase	**Tremor outcomes** with clonazepam with placebo Absolute results reported graphically Results after crossover	Reported as not significant Probably underpowered to detect a clinically important difference in outcomes	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [23]

Comment: We found no RCTs addressing long-term outcomes. Adverse effects with benzodiazepines, including dependency, sedation, and cognitive and behavioural effects, have been well described for other conditions.

OPTION DIAZEPAM New

- For GRADE evaluation of interventions for Essential tremor, see table, p 40 .
- We found no RCTs on the effects of diazepam in people with essential tremor of the hand.
- In general, benzodiazepines are associated with adverse effects such as dependency, sedation, and cognitive and behavioural effects.

Benefits and harms

Diazepam versus placebo:

We found no RCTs.

Comment: Adverse effects with benzodiazepines, including dependency, sedation, and cognitive and behavioural effects, have been well described for other conditions.

OPTION GABAPENTIN

- For GRADE evaluation of interventions for Essential tremor, see table, p 40 .
- We don't know whether gabapentin is useful in treating essential tremor of the hand, as studies were small and the results were inconsistent.
- We found no direct information about long-term outcomes of gabapentin in people with essential tremor.

Benefits and harms

Gabapentin versus placebo:

We found no systematic review. We found three small crossover RCTs. [24] [25] [26]

Tremor severity

Gabapentin compared with placebo Gabapentin may be more effective than placebo at improving some outcomes at up to 6 weeks in people with essential tremor of the hand, but studies were small and short term and results were inconsistent between trials (very low-quality evidence)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical scores					
[24] RCT **Crossover design** **3-armed trial**	16 people	**Tremor Clinical Rating Scale score , 2 weeks** with gabapentin (up to 1200 mg/day) with placebo Absolute results not reported Results before crossover The remaining arm evaluated propranolol (up to 120 mg/day)	Mean difference gabapentin *v* placebo: –3.03 P <0.05	○○○	gabapentin
[24] RCT **Crossover design** **3-armed trial**	16 people	**Disability score , 2 weeks** with gabapentin (up to 1200 mg/day) with placebo Absolute results not reported Results before crossover The remaining arm evaluated propranolol (up to 120 mg/day)	Mean difference gabapentin *v* placebo: –6.04 P = 0.04	○○○	gabapentin
[25] RCT **Crossover design**	20 people	**Clinical scores , 6 weeks** with gabapentin 1800 mg daily for 2 weeks with placebo for 2 weeks Results after crossover	Reported as not significant	⟷	Not significant
Accelerometry					
[26] RCT **Crossover design** **3-armed trial**	25 people	**Accelerometry scores, spirographs, or investigator global impression scores , 6 weeks** with gabapentin (1800 mg or 3600 mg daily) with placebo Results before crossover	Reported as not significant	⟷	Not significant
Self-rating scores					
[24] RCT **Crossover design** **3-armed trial**	16 people	**Self-evaluation , 2 weeks** with gabapentin (up to 1200 mg/day) with placebo Absolute results not reported Results before crossover The remaining arm evaluated propranolol (up to 120 mg/day)	Mean difference gabapentin *v* placebo: –1.37 P = 0.006	○○○	gabapentin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[26] RCT **Crossover design** **3-armed trial**	25 people	**Participants' global assessments , 6 weeks** with gabapentin (1800 mg or 3600 mg daily) with placebo Results before crossover	P <0.05	○○○	gabapentin
[25] RCT **Crossover design**	20 people	**Self-evaluation , 6 weeks** with gabapentin 1800 mg daily for 2 weeks with placebo for 2 weeks Results after crossover	Reported as not significant	⟷	Not significant
Performance tests					
[26] RCT **Crossover design** **3-armed trial**	25 people	**Scores of activities of daily living , 6 weeks** with gabapentin (1800 mg or 3600 mg daily) with placebo Results before crossover	P <0.005	○○○	gabapentin
[26] RCT **Crossover design** **3-armed trial**	25 people	**Water pouring scores , 6 weeks** with gabapentin (1800 mg or 3600 mg daily) with placebo Results before crossover	P <0.05	○○○	gabapentin
[25] RCT **Crossover design**	20 people	**Activities of daily living , 6 weeks** with gabapentin 1800 mg daily for 2 weeks with placebo for 2 weeks Results after crossover	Reported as not significant	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[24] [25] [26] RCT **Crossover design**	People with essential tremor	**Adverse effects** with gabapentin (up to 3600 mg daily *v* placebo)	The RCTs reported fatigue, drowsiness, nausea, dizziness, and decreased libido in people taking gabapentin		

Further information on studies

[26] The RCT found no significant difference between high and low doses of gabapentin in the 20 people who completed the trial.

Comment: The results of the three RCTs differ. It is unclear whether the difference arose by chance or whether confounding variables, such as prior use of antitremor medications, baseline severity, or assessment rating scales, explain the difference. We found no RCTs addressing long-term outcomes.

Clinical guide
Although the effect of gabapentin on essential tremor remains unclear, it may still be tried in patients with essential tremor who do not respond to other pharmacological therapy, or where other pharmacological therapy is contraindicated. The American Academy of Neurology has recommended that gabapentin (monotherapy) should be considered as probably effective in the treatment of limb tremor associated with essential tremor. [10]

OPTION LEVETIRACETAM New

- For GRADE evaluation of interventions for Essential tremor, see table, p 40 .
- We don't know whether levetiracetam is more effective than placebo at reducing symptoms in people with essential tremor.
- Evidence came from two very small RCTs, both of which were terminated early.

Benefits and harms

Levetiracetam versus placebo:

We found two small double-blinded RCTs, both of which were terminated early (see Further information on studies). [27] [28]

Tremor severity

Levetiracetam compared with placebo Levetiracetam may be no more effective than placebo at improving measures of tremor in people aged 35–83 years who have had long-standing essential tremor. However, evidence was very weak (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Tremor score					
[27] RCT **Crossover design**	15 people aged 35–83 years, with essential tremor, mean duration 35 years	**Mean Fahn-Tolosa-Marin Tremor Rating Scale total score** 37.5 with levetiracetam 34.8 with placebo	P = 0.113 The study was terminated early (see Further information on studies)	⟷	Not significant
[28] RCT **Crossover design**	12 people aged 67–81 years, with essential tremor, median duration 42 years	**Mean composite tremor score (summated from TRS Location/Severity, UTRA Specific Motor Task/Functions, and UTRA Tremor Functional Rating scales) reduction from baseline** –1.03 with levetiracetam –4.73 with placebo Results based on 10 people	P = 0.42 The RCT reported that no subject attained a clinically meaningful reduction in tremor severity of 30% The study was terminated early (see Further information on studies)	⟷	Not significant
Clinical scores					
[27] RCT **Crossover design**	15 people aged 35–83 years, with essential tremor, mean duration 35 years	**Examiner assessment of mean Global Disability (scale 0–4, where 0 = no functional disability to 4 = severe disability)** 1.80 with levetiracetam 1.67 with placebo	P = 0.302 The study was terminated early (see Further information on studies)	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[28] RCT **Crossover design**	12 people aged 67–81 years, with essential tremor, median duration 42 years	**Global evaluation by examiner (negative numbers = more tremor, positive numbers = improvement)** –2 with levetiracetam +9 with placebo Results based on 10 people	P = 0.19 The study was terminated early (see Further information on studies)	⟷	Not significant
Self-rating					
[27] RCT **Crossover design**	15 people aged 35–83 years, with essential tremor, mean duration 35 years	**Participant assessment of mean Global Disability (scale 0–4, where 0 = no functional disability to 4 = severe disability)** 1.80 with levetiracetam 1.67 with placebo	P = 0.352 The study was terminated early (see Further information on studies)	⟷	Not significant
[28] RCT **Crossover design**	12 people aged 67–81 years, with essential tremor, median duration 42 years	**Global evaluation by participant (negative numbers = more tremor, positive numbers = improvement)** 13 with levetiracetam 8 with placebo Results based on 10 people	P = 0.08 The study was terminated early (see Further information on studies)	⟷	Not significant
Accelerometry					
[28] RCT **Crossover design**	12 people aged 67–81 years, with essential tremor, median duration 42 years	**Accelerometry , maximum power** +179 with levetiracetam –73 with placebo Results based on 10 people	P = 0.25 The study was terminated early (see Further information on studies)	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[27] RCT **Crossover design**	15 people aged 35–83 years, with essential tremor, mean duration 35 years	**Adverse effects** with levetiracetam with placebo The most common adverse effects reported were increased tremor (5 with levetiracetam *v* 4 with placebo), drowsiness (4 *v* 0), depressed mood (3 *v* 0), and impaired balance or hearing (3 *v* 2; P value for comparisons of adverse effects not reported)			
[28] RCT **Crossover design**	12 people aged 67–81 years, with essential tremor, median duration 42 years	**Adverse effects** with levetiracetam with placebo The most common adverse effects reported were worse tremor (7 with levetiracetam *v* 2 with placebo), fatigue (5 *v* 1), drowsiness (4 *v* 2), and impaired bal-			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		ance (2 *v* 0; P value for comparisons of adverse effects not reported)			

Further information on studies

[27] The method of randomisation and allocation concealment was not described. Ten people took 1 or 2 additional drugs for tremor during the study (including propranolol, primidone, clonazepam, gabapentin, mirtazapine, and atenolol; further details not reported). Each drug period consisted of a 5-week titration phase, followed by a 4-week maintenance phase on the maximum tolerated dose, with a 3-week washout phase. It was planned to enrol 45 people, but enrolment was stopped when a blinded interim analysis of the first 15 people "revealed no possibility of efficacy". Three people dropped out during the levetiracetam phase due to: increased tremor, disequilibrium, drowsiness, and leg cramps; no improvement, mild depression, and fatigue; and increased tremor and anxiety. However, they were included in the analysis (last value carried forward).

[28] During the study, one concurrent anti-tremor medication was taken by seven people, two medications by two people, and four medications by one person. Each drug arm consisted of a 4-week titration phase, 2 weeks of stable dose (a target dose or lower maximal tolerated dose), and 4-week washout period. The study was discontinued at an interim analysis when the levetiracetim arm had a mean drop in the primary endpoint of about 3% compared with placebo of 11%. Three people withdrew during treatment with levetiracetam, compared with two people with placebo (P value not reported).

Comment: One RCT noted that at interim analysis, levetiracetam failed to demonstrate the 30% fall in tremor scores that was required; hence, it was unlikely to exert efficacy comparable to that of propranolol or primidone. [28] It noted that whether levetiracetam had a lower degree of anti-tremor potency was not assessed in the study.

OPTION LORAZEPAM New

- For GRADE evaluation of interventions for Essential tremor, see table, p 40 .
- We found no RCTs on the effects of lorazepam.
- In general, benzodiazepines are associated with adverse effects such as dependency, sedation, and cognitive and behavioural effects.

Benefits and harms

Lorazepam versus placebo:

We found no RCTs.

Comment: Adverse effects with benzodiazepines, including dependency, sedation, and cognitive and behavioural effects, have been well described for other conditions.

OPTION PHENOBARBITAL

- For GRADE evaluation of interventions for Essential tremor, see table, p 40 .
- We don't know whether phenobarbital is more effective than placebo at improving tremor in people with essential tremor of the hand. It improved some outcome measures but not others, and evidence was weak and inconsistent from three RCTs with small numbers.
- Phenobarbital is associated with depression, and with cognitive and behavioural adverse effects.

Benefits and harms

Phenobarbital versus placebo:

We found three small, short-term, crossover RCTs. [29] [30] [31]

Tremor severity

Phenobarbital compared with placebo We don't know whether phenobarbital (phenobarbitone) is more effective than placebo at improving symptoms at up to 5 weeks in people with essential tremor of the hand (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical scores					
[29] RCT **Crossover design** **3-armed trial**	17 people; 12/17 (70%) people completed the trial	**Clinical tremor scores , 4 weeks** with phenobarbital (phenobarbitone) with placebo Results after crossover Each treatment period was 4 weeks, total duration of 12 weeks The remaining arm evaluated propranolol No intention-to-treat analysis was performed	Reported as not significant	⟷	Not significant
[30] RCT **Crossover design** **3-armed trial**	16 people	**Clinical score and self-evaluation of tremor , 5 weeks** with phenobarbital with placebo Results before crossover The remaining arm evaluated primidone	Reported as not significant	⟷	Not significant
Accelerometry					
[31] RCT **Crossover design**	12 people	**Accelerometer recordings , 5 weeks** with phenobarbital with placebo	P <0.01	○○○	phenobarbital
[31] RCT **Crossover design**	12 people	**Proportion of people who responded (defined as decrease of 15% or more in tremor score measured by accelerometer)** 11/11 (100%) with phenobarbital 6/11 (55%) with placebo Results after crossover	Significance of the difference between groups not assessed		
Self-rating					
[31] RCT **Crossover design**	12 people	**Self-evaluation of tremor** with phenobarbital with placebo	No significant difference reported	⟷	Not significant
[31] RCT **Crossover design**	12 people	**Symptom rating scale , 5 weeks** with phenobarbital with placebo	P <0.05	○○○	phenobarbital

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Performance tests					
[29] RCT **Crossover design** **3-armed trial**	17 people; 12/17 (70%) people completed the trial	**Functional test scores , 4 weeks** with phenobarbital (phenobarbitone) with placebo Results after crossover Each treatment period was 4 weeks, total duration of 12 weeks The remaining arm evaluated propranolol No intention-to-treat analysis performed	Reported as not significant	⟷	Not significant
[31] RCT **Crossover design**	12 people	**Handwriting tests** with phenobarbital with placebo	No significant difference reported	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [29] [30] [31]

Comment: The RCTs were short term and small, and many randomised people did not complete the trials. Both phenobarbital and primidone (metabolised to phenobarbital) are associated with depression and cognitive and behavioural effects (particularly in children, older adults, and people with neuropsychiatric problems) and should be used with caution.

OPTION PRIMIDONE

- For GRADE evaluation of interventions for Essential tremor, see table, p 40 .
- Primidone may improve hand tremor in the short term (up to 10 weeks), but is associated with depression, and with cognitive and behavioural adverse effects.

Benefits and harms

Primidone versus placebo:

We found no systematic reviews. We found three small, brief crossover RCTs. [30] [32] [8]

Tremor severity

Primidone compared with placebo Primidone may be more effective than placebo at improving clinical scores, self-rating scores, and functional tests at 4–10 weeks in people with essential tremor of the hand (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical scores					
[30] RCT	16 people	**Clinical score and self-evaluation of tremor , 5 weeks**	P <0.05	○○○	primidone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Crossover design **3-armed trial**		with primidone with placebo Results after crossover The remaining arm evaluated phenobarbital (phenobarbitone)			
[32] RCT **Crossover design**	22 people Only 16/22 (73%) people completed the trial	**Clinical score (hand tremor) , 10 weeks** with primidone with placebo Results after crossover No intention-to-treat analysis was performed	P <0.02	○○○	primidone
Self-rating					
[32] RCT **Crossover design**	22 people Only 16/22 (73%) people completed the trial	**Self-evaluation (hand tremor) , 10 weeks** with primidone with placebo Results after crossover No intention-to-treat analysis was performed	P <0.01	○○○	primidone
Performance tests					
[8] RCT **Crossover design** **4-armed trial**	22 people	**Observer-rated score based on ability to write, feed, and function socially , 4 weeks** 5.2 with primidone 7.8 with placebo Results before crossover; 4 weeks' treatment, with a 2-week washout between treatments Scale: 0 = normal, 11 = unable to keep pencil on paper, needs help to feed, and no social activity The remaining arms evaluated alprazolam and acetazolamide	Significance of the difference between primidone and placebo not assessed		
[32] RCT **Crossover design**	22 people Only 16/22 (73%) people completed the trial	**Functional tests (hand tremor) , 10 weeks** with primidone with placebo Results after crossover No intention-to-treat analysis performed	P <0.01	○○○	primidone

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[32] RCT	22 people	**Adverse effects** with primidone with placebo			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Crossover design		5/22 (23%) people taking primidone withdrew because of adverse effects (first dose acute toxic reaction, sedation, daytime sleepiness, tiredness, and depression)			
[8] RCT **Crossover design** **4-armed trial**	22 people	**Adverse effects** with primidone with placebo 8/24 (33%) people receiving primidone discontinued treatment because of adverse effects, including nausea, ataxia, dizziness, or confusion The remaining arms evaluated alprazolam and acetazolamide			

Comment: The RCTs were short term and small, and many randomised people did not complete the trials. Both primidone and propranolol improve tremor by a magnitude of effect of about 50%. However, about 30% to 50% of essential tremor patients will not derive benefit from either. [33]

Clinical guide
Both primidone (metabolised to phenobarbital) and phenobarbital are associated with depression and cognitive and behavioural effects (particularly in children, older adults, and people with neuropsychiatric problems). Although primidone can be difficult to titrate in the early stages, it can be very helpful to people with essential tremor. Slow titration from a very low dose of primidone could help with initial side effects of dizziness and cognitive impairment.

OPTION PROPRANOLOL

- For GRADE evaluation of interventions for Essential tremor, see table, p 40 .
- We found several small RCTs, mostly of a crossover design, that only reported on results in the short term.
- Propranolol seems to effectively improve tremor severity (clinical scores, tremor amplitude, performance test scores, and self-evaluation of severity) compared with placebo in people with essential tremor (ET) of the hand.
- We found insufficient evidence about the effects of propranolol compared with other beta-blockers.
- Propranolol may be associated with adverse effects, including hypotension and depression. The potential benefits and adverse effects need to be discussed with the patient before treatment.

Benefits and harms

Propranolol versus placebo:

We found no systematic review, but we found 11 small, brief RCTs, many of which had a crossover design. [34] [35] [36] [17] [11] [37] [12] [29] [24] [13] [14]

Tremor severity

Propranolol compared with placebo Propranolol may be more effective than placebo at improving tremor severity (clinical scores, tremor amplitude, performance test scores, and self-evaluation of severity) at up to 6 weeks in people with ET of the hand (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical scores					
[34] RCT **Crossover design**	24 people with ET (23 completed), clinical diagnosis	**Clinical score (0–4) x segments , 2 weeks** 22/23 (96%) with propranolol 5/23 (22%) with placebo Results after crossover	P <0.001	○○○	propranolol
[35] RCT **Crossover design**	11 people with ET (10 completed), clinical diagnosis	**Clinical score , 6 weeks' treatment** with propranolol with placebo Absolute results not reported Results after crossover	P <0.003	○○○	propranolol
[36] RCT **Crossover design**	9 people with ET (7 completed), clinical diagnosis	**Clinical score** with propranolol with placebo Absolute results not reported Each treatment period was 1 week, total duration of 5 weeks (1st week, no treatment given) Results after crossover	P <0.01	○○○	propranolol
[11] RCT **Crossover design**	16 people with ET (16 completed), clinical diagnosis 15 of the participants in this RCT had previously participated in RCT [17]	**Clinical score** with propranolol 240 mg/day with placebo Absolute results reported graphically Propranolol and metoprolol were each given for two consecutive treatment periods (each lasting for 2 weeks) during which two dosage regimens were used: 120 and 240 mg daily for propranolol and 150 and 300 mg daily for metoprolol Results before crossover	P <0.05 (propranolol 240 mg/day *v* placebo)	○○○	propranolol 240 mg/day
[11] RCT **Crossover design**	16 people with ET (16 completed), clinical diagnosis 15 of the participants in this RCT had previously participated in RCT [17]	**Clinical score** with propranolol 120 mg/day with placebo Absolute results reported graphically Propranolol and metoprolol were each given for two consecutive treatment periods (each lasting for 2 weeks) during which two dosage regimens were used: 120 and 240 mg daily for propranolol and 150 and 300 mg daily for metoprolol Results before crossover	Unclear; no report of a significant difference (propranolol 120 mg/day *v* placebo)		
[37] RCT **Crossover design** **5-armed trial**	23 people with ET (15 completed), clinical diagnosis	**Clinical score (0–5 each side, maximum 10)** with propranolol 80 mg 3 times/day with propranolol LA 160 mg/day with propranolol LA 240 mg/day	P <0.05 (all doses of propranolol except 160 mg *v* placebo)	○○○	propranolol (80 mg 3 times/day or LA 240 mg/day or LA 320 mg/day)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with propranolol LA 320 mg/day with placebo Absolute results reported graphically Each treatment period was 3 weeks, total duration of 15 weeks Results after crossover			
[12] RCT **Crossover design** **4-armed trial**	9 people with ET (9 completed), clinical diagnosis	**Objective tremor score (0–25)** 6.6 with propranolol 10.7 with placebo The remaining arms evaluated sotalol and atenolol Results assessed after crossover; no washout period between drugs	P <0.01 (propranolol *v* placebo)	○○○	propranolol
[29] RCT **Crossover design** **3-armed trial**	17 people with ET (12 completed), clinical diagnosis	**Clinical score (0–10): mean change from baseline** –2.58 with propranolol –1.08 with placebo Four treatments given in 3 x 3 Latin squares; the remaining arm evaluated phenobarbital Results after crossover Each treatment period was 4 weeks, total duration of 12 weeks	P <0.01 (propranolol *v* placebo)	○○○	propranolol
[24] RCT **Crossover design** **3-armed trial**	16 people with ET (16 completed), clinical diagnosis	**Tremor Clinical Rating Scale score (P1 + P2, 0–78)** with propranolol with placebo Results after crossover Each treatment period was 2 weeks, with 1 week washout between treatments, total duration of 10 weeks The remaining arm evaluated gabapentin	Mean difference (propranolol *v* placebo): –4.95 P <0.01	○○○	propranolol
Accelerometry					
[34] RCT **Crossover design**	24 people with ET (23 completed), clinical diagnosis	**Accelerometry (frequency) , 2 weeks** with propranolol with placebo	Reported as unchanged		
[34] RCT **Crossover design**	24 people with ET (23 completed), clinical diagnosis	**Accelerometry (amplitude) , 2 weeks** with propranolol with placebo	P <0.001	○○○	propranolol
[36] RCT **Crossover design**	9 people with ET (7 completed), clinical diagnosis	**Accelerometry** with propranolol with placebo Each treatment period was 1 week, total duration of 5 weeks (1st week, no treatment given) Results after crossover	P <0.01	○○○	propranolol

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[17] RCT **Crossover design**	16 people with ET (16 completed), clinical diagnosis	**Accelerometry (amplitude)** with propranolol 120 and 240 mg/day with placebo Absolute results reported graphically Results after crossover, each treatment period was 4 weeks, total duration of 12 weeks	P <0.01 (propranolol 240 mg/day *v* placebo)	○○○	propranolol 240 mg/day
[11] RCT **Crossover design**	16 people with ET (16 completed), clinical diagnosis 15 of the participants in this RCT had previously participated in RCT [17]	**Accelerometry (amplitude)** with propranolol 120 mg/day with placebo Absolute results reported graphically Propranolol and metoprolol were each given for two consecutive treatment periods (each lasting for 2 weeks) during which two dosage regimens were used: 120 and 240 mg daily for propranolol and 150 and 300 mg daily for metoprolol Results before crossover	P reported as not significant (propranolol 120 mg/day *v* placebo)	⟷	Not significant
[11] RCT **Crossover design**	16 people with ET (16 completed), clinical diagnosis 15 of the participants in this RCT had previously participated in RCT [17]	**Accelerometry (amplitude)** with propranolol 240 mg/day with placebo Absolute results reported graphically Propranolol and metoprolol were each given for two consecutive treatment periods (each lasting for 2 weeks) during which two dosage regimens were used: 120 and 240 mg daily for propranolol and 150 and 300 mg daily for metoprolol Results before crossover	P <0.02 (propranolol 240 mg/day *v* placebo)	○○○	propranolol 240 mg/day
[37] RCT **Crossover design** **5-armed trial**	23 people with ET (15 completed), clinical diagnosis	**Accelerometry (magnitude)** with propranolol 80 mg 3 times/day with propranolol LA 160 mg/day with propranolol LA 240 mg/day with propranolol LA 320 mg/day with placebo Absolute results reported graphically Each treatment period was 3 weeks, total duration of 15 weeks Results after crossover	P <0.02 (all propranolol dosing regimens combined *v* placebo)	○○○	propranolol (all included dosing regimens combined *v* placebo)
[29] RCT **Crossover design** **3-armed trial**	17 people with ET (12 completed), clinical diagnosis	**Accelerometry (frequency: mean change from baseline)** –0.20 with propranolol +0.11 with placebo Four treatments given in 3 x 3 Latin squares; the remaining arm evaluated phenobarbital	P value reported as not significant	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Results after crossover Each treatment period was 4 weeks, total duration of 12 weeks			
[29] RCT **Crossover design** **3-armed trial**	17 people with ET (12 completed), clinical diagnosis	**Accelerometry (amplitude: mean change from baseline)** –87.60 with propranolol –66.90 with placebo Four treatments given in 3 x 3 Latin squares; the remaining arm evaluated phenobarbital Results after crossover Each treatment period was 4 weeks, total duration of 12 weeks	P <0.01	○○○	propranolol
[24] RCT **Crossover design** **3-armed trial**	16 people with ET (16 completed), clinical diagnosis	**Accelerometry (tremor magnitude)** with propranolol with placebo Results after crossover Each treatment period was 2 weeks, with 1 week washout between treatments, total duration of 10 weeks The remaining arm evaluated gabapentin	Reported as not significant P value not reported	⟷	Not significant
[24] RCT **Crossover design** **3-armed trial**	16 people with ET (16 completed), clinical diagnosis	**Accelerometry (tremor frequency** with propranolol with placebo Results after crossover Each treatment period was 2 weeks, with 1 week washout between treatments, total duration of 10 weeks The remaining arm evaluated gabapentin	Reported as not significant P value not reported	⟷	Not significant
[13] RCT **Crossover design** **3-armed trial**	24 people with ET (24 completed), clinical diagnosis	**Accelerometry (frequency)** 9.1 with propranolol for 5 to 7 days 9.4 with placebo for 5 to 7 days 1 week washout between treatments, total duration of 6 weeks Results after crossover The remaining arm evaluated pindolol for 5–7 days	Reported as not significant P value not reported	⟷	Not significant
[13] RCT **Crossover design** **3-armed trial**	24 people with ET (24 completed), clinical diagnosis	**Accelerometry (maximum amplitude)** 71 with propranolol for 5 to 7 days 128 with placebo for 5 to 7 days 1 week washout between treatments, total duration of 6 weeks Results after crossover The remaining arm evaluated pindolol for 5–7 days	P <0.05 (propranolol *v* placebo)	○○○	propranolol

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[14] RCT **Crossover design** **3-armed trial**	24 people with ET (24 completed), clinical diagnosis	**Accelerometry (tremor intensity, a summated value of the acceleration of postural tremor for 40 seconds)** 42.9 with propranolol 4.9 with placebo Results after crossover; 1 week crossover between drugs The remaining arm evaluated atenolol	P <0.01 (propranolol *v* placebo)	○○○	propranolol
Self-rating					
[34] RCT **Crossover design**	24 people with ET (23 completed), clinical diagnosis	**Self-rating** with propranolol with placebo 83% improved with propranolol, 75% of whom felt improvement was clinically important No self-rating reported for placebo Results after crossover			
[35] RCT	11 people with ET (10 completed), clinical diagnosis	**Self-rating , 6 weeks' treatment** 5/5 (100%) with propranolol 1/5 (20%) with placebo	P value not reported		
[36] RCT **Crossover design**	9 people with ET (7 completed), clinical diagnosis	**Number of people improved >2 assessments** 12 with propranolol 2 with placebo Each treatment period was 1 week, total duration of 5 weeks (1st week, no treatment given) Results after crossover Self-rating calculation compares assessments rather than participants, losing the benefits of randomisation	P <0.05	○○○	propranolol
[11] RCT **Crossover design**	16 people with ET (16 completed), clinical diagnosis 15 of the participants in this RCT had previously participated in RCT [17]	**Self-rating (0–5)** with propranolol 120 and 240 mg/day with placebo Absolute results reported graphically Propranolol and metoprolol were each given for two consecutive treatment periods (each lasting for 2 weeks) during which two dosage regimens were used: 120 and 240 mg daily for propranolol and 150 and 300 mg daily for metoprolol Results before crossover	P <0.01 (propranolol 120 mg/day or 240 mg/day *v* placebo)	○○○	propranolol
[37] RCT **Crossover design**	23 people with ET (15 completed), clinical diagnosis	**Self-rating (0–5)** with propranolol 80 mg 3 times/day with propranolol LA 160 mg/day	P <0.05 (all doses of propranolol *v* placebo)	○○○	propranolol

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
5-armed trial		with propranolol LA 240 mg/day with propranolol LA 320 mg/day with placebo Absolute results reported graphically Each treatment period was 3 weeks, total duration of 15 weeks Results after crossover			
[12] RCT **Crossover design** **4-armed trial**	9 people with ET (9 completed), clinical diagnosis	**Mean subjective tremor score (0–10)** 4.4 with propranolol 6.2 with placebo Results assessed after crossover; no washout period between drugs The remaining arms evaluated sotalol and atenolol	P = 0.1 (propranolol *v* placebo)	⟷	Not significant
[29] RCT **Crossover design** **3-armed trial**	17 people with ET (12 completed), clinical diagnosis	**Self-rating (0–10): mean change from baseline** –4.50 with propranolol –2.04 with placebo Four treatments given in 3 x 3 Latin squares; the remaining arm evaluated phenobarbital Results after crossover Each treatment period was 4 weeks, total duration of 12 weeks	P <0.01 (propranolol *v* placebo)	○○○	propranolol
[24] RCT **Crossover design** **3-armed trial**	16 people with ET (16 completed), clinical diagnosis	**Self-rating: subjective Disability Scale (25–100)** with propranolol with placebo Results after crossover Each treatment period was 2 weeks, with 1 week washout between treatments, total duration of 10 weeks The remaining arm evaluated gabapentin	Mean difference in Subjective Disability Scale score (propranolol *v* placebo) –4.48 P = 0.11	⟷	Not significant
Performance tests					
[35] RCT	11 people with ET (10 completed), clinical diagnosis	**Performance tests: pegboard test , 6 weeks' treatment** +2.9 with propranolol –2.1 with placebo Results after crossover	P = 0.06	⟷	Not significant
[11] RCT **Crossover design**	16 people with ET (16 completed), clinical diagnosis 15 of the participants in this RCT had previously participated in RCT [17]	**Performance tests (hand-writing, drawing geometrical figures, and tracing an Archimedes' spiral, scores 0–5)** with propranolol 120 and 240 mg/day with placebo Absolute results reported graphically	P <0.01 (propranolol 120 mg *v* placebo)	○○○	propranolol 120 mg

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Propranolol and metoprolol were each given for two consecutive treatment periods (each lasting for 2 weeks) during which two dosage regimens were used: 120 and 240 mg daily for propranolol and 150 and 300 mg daily for metoprolol Results before crossover			
[37] RCT **Crossover design** **5-armed trial**	23 people with ET (15 completed), clinical diagnosis	**Performance test scores (copy a short sentence and trace inside an Archimedes' spiral, 0–5)** with propranolol 80 mg three times/day with propranolol LA 160 mg/day with propranolol LA 240 mg/day with propranolol LA 320 mg/day with placebo Absolute results reported graphically Each treatment period was 3 weeks, total duration of 15 weeks Results after crossover	P <0.01 (propranolol and propranolol LA 320 mg *v* placebo)	○○○	propranolol (80 mg/day three times/day or LA 320 mg/day)
[29] RCT **Crossover design** **3-armed trial**	17 people with ET (12 completed), clinical diagnosis	**Performance tests: mean change from baseline in pegboard test (time to complete in seconds)** –8.58 with propranolol –6.17 with placebo Four treatments given in 3 x 3 Latin squares; the remaining arm evaluated phenobarbital Results after crossover Each treatment period was 4 weeks, total duration of 12 weeks	P value reported as not significant	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [34] [35] [36] [17] [11] [37] [12] [29] [24] [13] [14]

Propranolol versus other beta-blockers:

See Beta-blockers other than propranolol, p 6 .

Further information on studies

[36] Withdrawals (mainly because of fatigue and bradycardia) were uncommon (e.g., 1/10 [10%] people in this RCT).

[34] [35] [36] [17] [11] [37] [12] [29] [24] [13] [14] Depression, diarrhoea, breathlessness, sedation, blurred vision, and sexual problems were each reported in less than 5% of people taking propranolol.

Comment: We found no placebo-controlled RCTs addressing long-term outcomes. All trials were analysed as 'on treatment' rather than by intention to treat, and this may have biased results. Accelerometry is a proxy outcome that was reported in several RCTs. Accelerometry (amplitude) results were mostly in favour of propranolol. Propranolol did not change tremor frequency but rather dampened the tremor amplitude and provided clinical benefits (including improvements in activities of daily living). Patients are more likely to be disabled from the tremor amplitude (unable to hold on to things and dropping things, etc) rather than tremor frequency. Some small RCTs did not find statistical significant benefits for propranolol. However, overall, there was a trend towards clinical benefits with propranolol compared with placebo in these studies, which might have been underpowered to detect statistical significance. In addition, a moderate proportion of patients did not respond to propranolol, highlighting that ET is a heterogeneous disorder. Both primidone and propranolol improve tremor by a magnitude of effect of about 50%. About 30% to 50% of people with ET will not get benefit from either, however. [33] People with congestive heart failure, second-degree heart block, asthma, severe allergy, and insulin-dependent diabetes were generally excluded from the RCTs. All of the studies were small. The possibility of publication bias has not been excluded.

Clinical guide
There is a risk of depression in patients taking propranolol. Propranolol should be used with caution in patients with certain respiratory problems, such as asthma and chronic obstructive pulmonary disease. In addition, beta-blockers can worsen severe congestive heart failure and mask the catecholamine responses to hypoglycaemia in diabetic patients.

OPTION SODIUM OXYBATE New

- For GRADE evaluation of interventions for Essential tremor, see table, p 40 .
- We found no RCTs on the effects of sodium oxybate in people with essential tremor of the hand.

Benefits and harms

Sodium oxybate versus placebo:

We found no RCTs.

Comment: None.

OPTION TOPIRAMATE

- For GRADE evaluation of interventions for Essential tremor, see table, p 40 .
- Topiramate appears to improve clinical rating scales for hand tremor in the short term in people with essential tremor of the hand, but is associated with frequent adverse effects.

Benefits and harms

Topiramate versus placebo:

We found three RCTs, one with parallel [38] and two with crossover [39] [40] design.

Tremor severity

Topiramate compared with placebo Topiramate may be more effective than placebo at improving observer-rated tremor scores between 6 and 24 weeks in people with essential tremor of the hand (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Tremor score/improvement					
[38] RCT	223 people with moderate to severe essential tremor of the hands or forearms About half of participants also took one other antitremor drug; dose had to remain stable throughout the trial	**Mean reduction in tremor score , 24 weeks** –10.8 with topiramate –5.8 with placebo Overall tremor score was derived from combining scores for upper limb tremor amplitude, motor tasks, and functional disabilities	P <0.001 Calculations adjusting for the use of other antitremor medication found that this did not impact the results	○○○	topiramate
[39] RCT **Crossover design**	24 people with tremor of hand, head, or voice	**Observer-rated tremor score improvement , 6 weeks after crossover** 0.88 with topiramate 0.15 with placebo 2 weeks' treatment with a 2-week washout between treatments	P = 0.015	○○○	topiramate
[40] RCT **Crossover design**	16 people with definitive or probable essential tremor involving the hand, head, or voice Results after crossover in 10 people who completed the trial, taking into account the period effect and treatment period interaction, which did not significantly alter outcomes (P >0.05)	**Proportion of people who improved , 6 weeks** 4/10 (40%) with topiramate 0/10 (0%) with placebo Outcomes were assessed using accelerometer recording, spirography, and activities of daily living	Reported as not significant P value not reported The RCT was underpowered to detect a clinically important difference between groups	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[38] RCT	223 people with moderate to severe essential tremor of the hands or forearms About half of participants also took one other antitremor drug; dose had to remain stable throughout the trial	**Proportion of people who withdrew because of adverse effects** 32% with topiramate 10% with placebo The most common adverse effects associated with topiramate were difficulty in concentrating, confusion, nausea, dyspepsia, appetite decrease, taste perversion, psychomotor slowing, somnolence, fatigue, and paraesthesia	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[38] RCT	223 people with moderate to severe essential tremor of the hands or fore-arms About half of partic-ipants also took one other an-titremor drug; dose had to remain sta-ble throughout the trial	**Mean reduction in body weight** 3.6 kg with topiramate 0.6 kg with placebo	P <0.001	○○○	placebo
[39] RCT **Crossover design**	24 people with tremor of hand, head, or voice	**Proportion of people who withdrew because of adverse effects** 5/24 (21%) with topiramate 1/24 (4%) with placebo The most common adverse ef-fects with topiramate were ap-petite suppression, weight loss, and paraesthesia			

No data from the following reference on this outcome. [40]

Comment: We found no RCTs addressing long-term outcomes.

Clinical guide
Topiramate is useful in the treatment of tremor but hampered by side effects. It cannot be used in patients who are prone to urinary stones and who are allergic to sulfa. However, in a sub-analysis of a larger study, [41] significant improvements were noted with topiramate use in doses of 100 mg/day, which means that patients might not need to titrate up to large doses. It does not carry the side effects of depression and orthostatic hypotension. The clinical evidence for topiramate to treat essential tremor is less robust than that for propranolol and primidone, and it might be used as a second-line therapy. In addition, topiramate also has different side effect profiles from propra-nolol and primidone. Topiramate also has migraine prophylaxis effects and could be beneficial for patients with essential tremor and comorbid migraine. In certain patients, appetite suppression and weight loss might be seen as beneficial effects of topiramate. Topiramate should be used with caution in patients with a history of angle closure glaucoma and calcium phosphate nephrolithiasis.

GLOSSARY

Accelerometry Recording of the movements from a body segment to allow measurement of frequency, amplitude, or intensity of a tremor. Intensity of tremor is a measure of the overall magnitude of movement; it often refers to the product of the amplitude of tremor multiplied by its frequency.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Alprazolam New option. Two RCTs added that were included in a previous version of this overview. [8] [9] Categorised as 'unknown effectiveness'.

Clonazepam New option. One RCT added that was included in a previous version of this overview. [23] Categorised as 'unknown effectiveness'.

Diazepam New option. No evidence found. Categorised as 'unknown effectiveness'.

Levetiracetam New option. Two RCTs added. [27] [28] Categorised as 'unknown effectiveness'.

Lorazepam New option. No evidence found. Categorised as 'unknown effectiveness'.

Sodium oxybate New option. No evidence found. Categorised as 'unknown effectiveness'.

Beta-blockers other than propranolol Evidence re-evaluated. No new evidence found. Categorisation unchanged (unknown effectiveness).

Botulinum A toxin-haemagglutinin complex Evidence re-evaluated. Categorisation unchanged (trade-off between benefits and harms).

Gabapentin Evidence re-evaluated. No new evidence found. Categorisation unchanged (unknown effectiveness).

Phenobarbital Evidence re-evaluated. No new evidence found. Categorisation changed from 'trade-off between benefits and harms' to 'unknown effectiveness'.

Primidone Evidence re-evaluated. No new evidence found. Categorisation changed from 'trade-off between benefits and harms' to 'likely to be beneficial'.

Propranolol Evidence re-evaluated. No new evidence found. Categorisation unchanged (likely to be beneficial).

Topiramate Evidence re-evaluated. No new evidence found. Categorisation unchanged (trade-off between benefits and harms).

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Disclaimer

GRADE **Evaluation of interventions for Essential tremor.**

Important outcomes					Tremor severity				
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consis-tency**	**Direct-ness**	**Effect size**	**GRADE**	**Comment**
What are the effects of drug treatments in people with essential tremor of the hand?									
2 (46) [8] [9]	Tremor severity	Alprazolam versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results; directness point deducted for no statistical analysis between groups (baseline analysis)
6 (107) [11] [12] [13] [14] [15] [16]	Tremor severity	Beta-blockers other than propranolol versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, poor follow-up, incomplete reporting of results, and weak methods
5 (247) [11] [12] [14] [18] [19]	Tremor severity	Beta-blockers other than propranolol versus propranolol	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and weak methods (no washout period, low follow up); directness point deducted for no statistical analysis between groups in some RCTs
2 (158) [20] [21]	Tremor severity	Botulinum A toxin-haemagglutinin complex versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results; directness point deducted for unclear population (people in 1 RCT were unresponsive to medical therapy, but this was not defined)
1 (6) [23]	Tremor severity	Clonazepam versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and poor follow-up
3 (unclear, less than 61) [24] [25] [26]	Tremor severity	Gabapentin versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results; directness point deducted for conflicting results (possible confounding variables)
2 (25) [27] [28]	Tremor severity	Levetiracetam versus placebo	4	–2	0	–2	0	Very low	Quality points deducted for weak methods and sparse data; directness points deducted for early termination of trials and use of concomitant medication
3 (45) [29] [30] [31]	Tremor severity	Phenobarbital versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and weak methods (no intention-to-treat analysis, and high withdrawals)
3 (60) [30] [32] [8]	Tremor severity	Primidone versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and weak methods (no intention-to-treat analysis, and high withdrawals)
11 (less than 189) [34] [35] [36] [17] [11] [37] [12] [29] [24] [13] [14]	Tremor severity	Propranolol versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and weak methods ('on treatment' and no intention-to-treat analysis, short term [6 weeks], possible publication bias)
3 (263) [38] [39] [40]	Tremor severity	Topiramate versus placebo	4	–1	0	–1	0	Low	Quality point deducted for weak methods (unclear population [definitive or probable essential tremor], poor follow-up, composite outcome score); directness point deducted for use of co-interventions

Important outcomes			Tremor severity						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consis-tency	Direct-ness	Effect size	GRADE	Comment
We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.									